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GAUGING THE SAFETY AND EFFICACY OF NITROGLYCERINE USED TRANSDERMALLY AS A TOCOLYTIC AGENT IN FEMALES WITH PRETERM LABOR

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ABSTRACT

Background: Preterm birth has been a common concern with increasing incidence globally and is a continuous challenge for Obstetricians. Preterm birth is seen to be complicating nearly 8-10% of the birth rate. The etiology of preterm birth is still unknown and the associated burden is quite high.

Aim: To assess the safety and efficacy of Nitroglycerine used transdermally as a tocolytic agent in females with preterm labor.

Methods: The present prospective clinical study assessed 200 females having preterm labor. These 200 females were divided into two groups with 100 subjects each which were randomly divided into bed rest alone or the Nitroglycerine patch group. The study was done for 6 months period.

Results: Pregnancy was prolonged by <48 hours in 6% (n=6) subjects, by 48-72 hours in 8% (n=8) subjects, 73-96 hours in 22% (n=22) subjects, and by ≥7 days in 56% (n=56) study subjects. Tocolysis induced in 100 Group I subject was successful in 94% (n=94) subjects and was unsuccessful in 6% (n=6) study subjects. The resuscitation needs and Apgar scores of <7 at 5 minutes were significantly lesser in Group I with p=0.02 for both. The number of Low-birth-weight subjects with a weight of ≤1.8 kg and 1.9-2.1 kg was significantly lesser in group I with 10 and 14 subjects compared to Group II subjects where it was 16 and 34 subjects

Conclusion: The present study concludes that Nitroglycerine used transdermally in females with preterm labor has equal efficacy as other commonly used tocolytic agents. Nitroglycerine is a drug of choice for the acute relaxation of the uterus in subjects with preterm labor.

Keywords: Nitroglycerine, preterm labor, ritodrine, tocolytics, transdermal nitroglycerine

INTRODUCTION

The onset of labor after the 20-24 weeks of gestational age and before the completion of 37 weeks of pregnancy is termed PTL (preterm labor).[1] The exact mechanism and etiology of preterm labor are unknown and not clear, the most commonly associated with the untimely or early start of the normal and physiological uterine contraction or any pathology causing uterine contraction which leads to preterm deliveries in the affected subjects.[2] Preterm birth depicts a serious public health concern affecting nearly 7% to 12% of pregnant females resulting in approximately 7-% to 80% mortality and morbidity in neonates. After 34 weeks of gestation, survival rates are better owing to advancements in feto-maternal medicine in the recent past.[3]

Majority of the neonatal deaths are attributed to intraventricular hemorrhage, respiratory distress syndrome, retinopathy of prematurity, periventricular leukomalacia, necrotizing enterocolitis, sepsis, and patent ductus arteriosus.[4] In long-term studies, it is seen that there is more risk of giving birth to neurodevelopmental handicaps with blindness, hearing loss, and cerebral palsy in neonates with preterm birth. Also, various

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intellectual impairments are seen in preterm neonates. Long-term sequelae of non-neurological origin can be a compromise in the overall growth of neonates and chronic pulmonary diseases.[5]

The treatment of preterm labor is mainly focused on the tocolytic agents which allow the antenatal corticosteroid administration to improve the lung maturity of the fetus and allow transfer of the mothers to a tertiary care center having a NICU (neonatal intensive care unit).[6] Nitroglycerine is a drug having a high first-pass inactivation in the liver. The active substance of nitroglycerine is metabolized swiftly in the liver by an enzyme, glutathione-dependent organic nitrate reductase. To pass this metabolism, transdermal use of nitroglycerine is advised in cases with preterm labor which allow the drug delivery at a predictable and constant rate to allow the drug to reach a smooth plasma concentration without any fluctuations.[7] The present study aimed to assess the safety and efficacy of Nitroglycerine used transdermally as a tocolytic agent in females with preterm labor.

MATERIALS AND METHODS

The present prospective randomized controlled clinical study was done to assess the safety and efficacy of Nitroglycerine used transdermally as a tocolytic agent in females with preterm labor. The study was done at Department of Obstetrics and Gynecology, Guru Govind Singh Hospital, Delhi, after the clearance was obtained from the concerned ethical committee. After explaining the detailed study design, informed consent was taken from all the subjects in both verbal and written format.

The study included 200 females with preterm labor who were randomly divided into two groups of 100 subjects each where Group I subject were given transdermal nitroglycerine patch and Group II subjects were advised bed rest for preterm labor. The subjects were blinded to the treatment provided to them.

The inclusion criteria for the study were subjects with intact membranes, cervical dilatation of up to 3 cm, 80% or more of progressive cervical effacement, having 2 contractions in 10-minutes with each contraction lasting for 40 seconds, assessed on ultrasonography and clinical examination, and subjects having the gestational age between 28 weeks to 34 weeks. The exclusion criteria for the study of fetal factors include erythroblastosis, oligohydramnios, polyhydramnios, congenital anomalies, IUGR (intra-uterine growth restriction), fetal distress, fetal death, and multiple gestations. The maternal factors considered for exclusion were subjects with ARDS (acute respiratory distress syndrome), asthmatics, having pulmonary or renal disorders, previous cesarean section, cardiac disease, hypertension, pregnancy-induced hypertension, antepartum hemorrhage, cervical dilatation of >3cm, infection, and membrane rupture.

After final inclusion, detailed history was recorded for all the subjects followed by a clinical examination. The data recorded were gender, age, medical history, and menstrual history. The investigations done were ultrasound, vaginal swab, complete blood counts, and urine analysis. Group I participants were given a transdermal nitroglycerine patch (NTG-10) releasing nitroglycerine at a rate of 10mg every 24 hours. The patch was placed on the abdominal wall. When no contraction change is seen or contractions increased in duration, frequency, or intensity after 1 hour of patch placement, an additional patch of the same dose was given to the subjects and both patches were kept for 24 hours. Treatment was discontinued if uterine contraction continued for >24 hours even after 20 mg of nitroglycerine patch application, subjects with PROM (premature rupture of membrane), pulse rate >100/min, and blood pressure falls below 90/60 mmHg. Group II subjects were advised the bed rest. Subjects from both groups were given two doses of 12 mg Betamethasone intramuscular (IM) at an interval of 24 hours are given.

The maternal outcomes assessed were adverse drug reactions, delivery mode, gestational age at delivery, complete course of maternal steroids, pregnancy prolongation duration, successful tocolysis assessed as tocolysis for >48 hours, and uterine contraction subsides. The fetal outcomes assessed in the study were neonatal death and admission to NICU (neonatal ICU).

The data collected were assessed statistically using logistic regression and multivariate statistical techniques. The data were presented in tabulated and descriptive formats. SPSS version 22.0, 2013, Armonk, NY: IBM Corp and chi-square and Fisher exact test were utilized. The data were expressed as mean and standard deviations and as percentages and numbers with a 0.05% significance level.

RESULTS

The study included 200 females with preterm labor who were randomly divided into two groups of 100 subjects each where Group I subject were given transdermal nitroglycerine patch and Group II subjects were advised bed rest for preterm labor. The mean age of Group I and II were comparable with 28.86±6.36 and 27.58±5.71 years

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respectively with p=0.27. The complete course of steroids between Group I and II females was comparable with p=0.21. The majority of Group I subjects was of gestational age of 29-32 weeks with 64% (n=64) subjects and 62% (n-=62) subjects of Group II. Gestational age was also comparable with p=0.56. Previous abortion was done in 46% (n=46) subjects and 40% (n=40) subjects from Groups I and II respectively with p=0.53. Preterm labor history was positive in 10% (n=10) and 4% (n=4) subjects of groups I and II with p=0.42. Parity was also comparable between the two groups with p=0.48 (Table 1).

For the laboratory parameters, hemoglobin was 11.85±0.94 and 11.81±0.99 gm/dl in Groups I and II which was non-significant with p=0.82. The creatinine was also comparable with respective values of 0.83±0.17 and 0.82±0.12 mg/dl in groups I and II respectively with p=0.7. Mean urea in Groups I and II were 29.98±9.06 and 27.88±8.15 mg/dl respectively with p=0.25. Urine culture was positive in 10% (n=10) and 8% (n=8) subjects of groups I and II respectively which was non-significant with p=1.00. Vaginal culture was positive in 6% (n=6) and 10% (n=10) study subjects with p=0.74. Rh factor was positive for 40% (n=40) subjects of group I and 56% (n=56) group II subjects with p=0.13. ABO grouping was also comparable between the two groups with p=0.33 as shown in Table 2.

Concerning the maternal outcomes in the Group I subject managed with nitroglycerine, it was seen that pregnancy was prolonged by <48 hours in 6% (n=6) subjects, by 48-72 hours in 8% (n=8) subjects, 73-96 hours in 22% (n=22) subjects, and by ≥7 days in 56% (n=56) study subjects. Tocolysis induced in 100 Group I subject was successful in 94% (n=94) subjects and was unsuccessful in 6% (n=6) study subjects. The side-effect of nitroglycerine for tocolysis was assessed, and it was seen that no side-effect was seen in 66% (n=66) subjects, patch site irritation in 4% (n=4) study subjects, vomiting in 6% (n=6) study subjects, hypotension in 10% (n=10) study subjects, and headache in 14% (n=14) study subjects respectively as depicted in Table 3.

On assessing the fetal outcomes in the two groups of study subjects, it was seen that fetal mortality was seen in 6% (n=6) and 16% (n=16) study subjects respectively which were comparable in the two groups (p=0.13). Mechanical ventilation was needed in 6% (n=6) and 12% (n=12) subjects from groups I and II respectively (p=0.47) which was also comparable. The need for admission to ICU and ARDS was also comparable between the two groups with respective p-values of 0.47 and 0.18 respectively. The resuscitation need was significantly lesser in Group I with 6% (n=6) subjects with nitroglycerine and 22% (n=22) subjects on bed rest with p=0.02. Apgar scores of <7 at 5 minutes were also seen in a significantly lesser fetus with 6% (n=6) subjects of Group I and in 22% (n=22) subjects from Group II which was significantly higher with p=0.02. The number of Low-birth-weight subjects with a weight of ≤1.8 kg and 1.9-2.1 kg was significantly lesser in group I with 10 and 14 subjects compared to Group II subjects where it 16 and 34 subjects as shown in Table 4.

DISCUSSION

The study included 200 females with preterm labor who were randomly divided into two groups of 100 subjects each where Group I subject were given transdermal nitroglycerine patch and Group II subjects were advised bed rest for preterm labor. The mean age of Group I and II were comparable with 28.86±6.36 and 27.58±5.71 years respectively with p=0.27. The complete course of steroids between Group I and II females was comparable with p=0.21. The majority of Group I subjects was of gestational age of 29-32 weeks with 64% (n=64) subjects and 62% (n-=62) subjects of Group II. Gestational age was also comparable with p=0.56. Previous abortion was done in 46% (n=46) subjects and 40% (n=40) subjects from Groups I and II respectively with p=0.53. Preterm labor history was positive in 10% (n=10) and 4% (n=4) subjects of groups I and II with p=0.42. Parity was also comparable between the two groups with p=0.48. These data were compared to the studies of Bashir B et al[8] in 2019 and Baker E et al[9] in 2015 where authors assessed subjects with demographics comparable to the present study.

On assessing the laboratory parameters, hemoglobin was 11.85±0.94 and 11.81±0.99 gm/dl in Groups I and II which was non-significant with p=0.82. The creatinine was also comparable with respective values of 0.83±0.17 and 0.82±0.12 mg/dl in groups I and II respectively with p=0.7. Mean urea in Groups I and II were 29.98±9.06 and 27.88±8.15 mg/dl respectively with p=0.25. Urine culture was positive in 10% (n=10) and 8% (n=8) subjects of groups I and II respectively which was non-significant with p=1.00. Vaginal culture was positive in 6% (n=6) and 10% (n=10) study subjects with p=0.74. Rh factor was positive for 40% (n=40) subjects of group I and 56% (n=56) group II subjects with p=0.13. ABO grouping was also comparable between the two groups with p=0.33. These findings were consistent with the studies of Pimenta JM et al[10] in 2018 and Tavassoli F et

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al[11] in 2020 where authors suggested comparable blood urea, creatinine, positive vaginal and urine culture, and ABO grouping as of the present study.

The study results showed that the maternal outcomes in the Group I subject managed with nitroglycerine, it was seen that pregnancy was prolonged by <48 hours in 6% (n=6) subjects, by 48-72 hours in 8% (n=8) subjects, 73-96 hours in 22% (n=22) subjects, and by ≥7 days in 56% (n=56) study subjects. Tocolysis induced in 100 Group I subject was successful in 94% (n=94) subjects and was unsuccessful in 6% (n=6) study subjects. The side-effect of nitroglycerine for tocolysis was assessed, and it was seen that no side-effect was seen in 66% (n=66) subjects, patch site irritation in 4% (n=4) study subjects, vomiting in 6% (n=6) study subjects, hypotension in 10% (n=10) study subjects, and headache in 14% (n=14) study subjects respectively. These results were in agreement with the studies of Goyal N et al[12] in 2020 and Kaur P et al[13] in 2021 where authors reported high success of nitroglycerine tocolysis with increased pregnancy duration and lesser side effects which were similar to the present study results.

Concerning the fetal outcomes in the two groups of study subjects, it was seen that fetal mortality was seen in 6% (n=6) and 16% (n=16) study subjects respectively which were comparable in the two groups (p=0.13). Mechanical ventilation was needed in 6% (n=6) and 12% (n=12) subjects from groups I and II respectively (p=0.47) which was also comparable. The need for admission to ICU and ARDS was also comparable between the two groups with respective p-values of 0.47 and 0.18 respectively. The resuscitation need was significantly lesser in Group I with 6% (n=6) subjects with nitroglycerine and 22% (n=22) subjects on bed rest with p=0.02. Apgar scores of <7 at 5 minutes were also seen in a significantly lesser fetus with 6% (n=6) subjects of Group I and in 22% (n=22) subjects from Group II which was significantly higher with p=0.02. The number of Low-birth-weight subjects with a weight of ≤1.8 kg and 1.9-2.1 kg was significantly lesser in group I with 10 and 14 subjects compared to Group II subjects where it 16 and 34 subjects. These results were in line with the previous studies of Jamil M et al[14] in 2020 and Akhtar Z et al[15] in 2020 where authors reported similar fetal outcomes the following nitroglycerine as of the present study as reported by the authors in their respective studies.

CONCLUSION

Considering its limitations, the present study concludes that Nitroglycerine used transdermally in females with preterm labor has equal efficacy as other commonly used tocolytic agents. Nitroglycerine is a drug of choice for the acute relaxation of the uterus in subjects with preterm labor. Also, transdermal nitroglycerine was found to be a non-invasive, cost-effective, well-tolerated, effective, safe, and promising mode of tocolysis. The limitations of this study were smaller considered population, shirt monitoring, and biased related to the geographic location warranting further long-term studies planned longitudinally.

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TABLES

Characteristics	**Group I (nitroglycerine group) % (n=100)**	**Group II (bed rest) % (n=100)**	**p-value**
Mean age (years)	28.86±6.36	27.58±5.71	0.27
Complete course of steroids (>34 weeks)	78 (78)	66 (66)	0.21
Gestational age at delivery (weeks)			
29-32	64 (64)	62 (62)	0.56
33-34	12 (12)	18 (18)	
35-37	20 (20)	16 (16)	
>37	2 (2)	0	
Abortion history			
Yes	46 (46)	40 (40)	0.53
No	54 (54)	60 (60)	
Preterm labor history			
Yes	10 (10)	4 (4)	0.42
No	90 (90)	96 (96)	
Parity			
0 (primigravida)	18 (18)	24 924)	0.48
1	16 (16)	16 (16)	
2	20 (20)	28 (28)	
≥3	46 946)	32 (32)	

Table 1: Demographic characteristics of the study participants

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Laboratory investigations	Group I (nitroglycerine group) % (n=100)	Group II (bed rest) % (n=100)	p-value
Hemoglobin (gm/dl)	11.85±0.94	11.81±0.99	0.82
Creatinine (mg/dl)	0.83±0.17	0.82±0.12	0.7
Urea (mg/dl)	29.98±9.06	27.88±8.15	
Urine culture			
Positive	10 (10)	8 (8)	1.00
Negative	90 (90)	92 (92)	
Vaginal culture			
Positive	6 (6)	10 (10)	0.74
Negative	94 (94)	90 (90)	
ABO group			
A	24 (24)	22 (22)	0.33
B	28 (28)	26 (26)	
AB	14 (14)	28 (28)	
O	34 (34)	24 (24)	
Rh Factor			
Positive	40 (40)	56 (56)	0.13
Negative	60 (60)	44 (44)	

Table 2: Laboratory investigations in the two groups of study subjects

Maternal Outcome with nitroglycerine	%	N
Duration of pregnancy prolongation		
<48 hours	6	6
48-72 hours	8	8
73-96 hours	22	22
97-<7 days	8	8
≥7 days	56	56
Tocolysis success		
Success	94	94
Failure	6	6
Nitroglycerine side-effects		
None	66	66
Patch site irritation	4	4
Vomiting	6	6
Hypotension	10	10
Headache	14	14

Table 3: Maternal outcomes with nitroglycerine patch in Group I subjects

Fetal Outcome with nitroglycerine	Group I % (n=100)	Group II % (n=100)	N
Death	6 (6)	16 (16)	0.13
Mechanical ventilation need	6 (6)	12 (12)	0.47
NICU admission	6 (6)	12 (12)	0.47
ARDS	4 (4)	14 (14)	0.18
Required resuscitation	6 (6)	22 (22)	0.02
Apgar score <7 at 5 minutes	6 (6)	22 (22)	0.02
Birth weight (kg)			
≤1.8	10 (10)	16 (16)	0.001
1.9-2.1	14 (14)	34 (34)	
2.2-2.4	36 (36)	34 (34)	
>2.4	40 (40)	16 (16)	

Table 4: Fetal outcomes in the two groups of study subjects